REMARKS

The Telephone Interview

The undersigned greatly appreciated the opportunity to discuss this application with the new examiner and supervisor. As discussed, the technology is very important since this provides a means to achieve replacement heart components that NO other technology can: a tissue engineered heart component(s) that (1) incorporates fully into the patient, (2) provides comparable biomechanical properties as the component(s) being replaced, and (3) GROWS with the patient.

The features are completely unexpected, not just in view of the prior art, but in view of the general knowledge in the field. The priority date of the application that originally issued as U.S. Patent No. 6,348,069, is May 19, 1995. Further studies were conducted and published by the inventors. Attached are copies of publications reporting the results of these studies:

Breuer, et al., "Tissue Engineering Lamb Heart Valve Leaflets" Biotech. Bioeng. 50:562-567 (1996)

Zund, et al., "The in vitro construction of a tissue engineered bioprosthetic heart valve" Eur. J. Cardio-thoracic Surg. 11:493-497 (1997)

Hoerstrup, et al., "Functional Living Trileaflet Heart Valves Grown in vitro" Circulation 102; III-44-III-49 (2000).

Sodian, et al., "Early In vivo Experience with Tissue-Engineered Trileaflet Heart Valves" Circulation 102; III-22-III-29 (2000)

Stock, et al., "Tissue Engineering of Heart Valves- Current Aspects" Thorac. Cariov. Surg. 50:184-193 (2002)

To more clearly define the structural features of the claimed matrix and method of making, amendments have been made to the claims to emphasize:

(1) the matrix is made of a synthetic biodegradable polymer which provides the biomechanical properties of the final construct (the heart valve or leaflet) until the seeded cells can lay down their own extracellular matrix (patent col. 3, lines 14-20; patent col. 5, lines 8-19) and

(2) the matrix is in the shape of the tissue engineered construct (i.e., heart valve or leaflet) so that the cells attach to and proliferate on it to the edges of the matrix (patent col. 3, lines 20-24; lines 62-66).

None of the art recognizes either the importance of both of these features. None would lead one of ordinary skill in the art to have a reasonable expectation of a cell-construct that could actually form tissue at a site with such high demands for mechanical properties *even as the polymer degrades, up until the cells have grown to confluence and laid down an extracellular matrix.*

New claim 18 requires the matrix to be cultured in a bioreactor to form a fibrous implant prior to implantation; new claim 19 is where this is in an animal. Support is found in the patent at col. 7, lines 12-16. See also claim 3 where it is first implanted at a site in the host different from the final site of implantation.

Claims 8, 10 and 15-18 have been cancelled in view of the amendments to the claims and the restriction requirement. The claims to the cell-matrix per se are being pursued in a divisional.

Rejections under 35 U.S.C. 103

Claims 1-5, 8-11, 15/1, 15/2, 15/3, 15/4, 15/5, 15/8, 15/9, 15/10, 15,11 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 5,514,378 to Mikos ("Mikos") in view of U.S. Patent No. 3,514,791 to Sparks ("Sparks") or U.S. Patent No. 4,795,459 to Jauregui ("Jauregui"). Claims 12-14, 15/12, 15/13, 15/14 were rejected under 35 U.S.C. 103 as obvious unpatentable under 35 U.S.C. § 103(a) over Mikos in view of Sparks or Jauregui further in view of U.S. Patent No. 5,709,854 to Griffith-Cima, et al. ("Griffith-Cima"). Claims 1-5 and 8-15 are unpatentable under 35 U.S.C. § 103(a) over Sparks in view of Mikos or Griffith and in view of either Jauregui or U.S. Patent No. 4,916,193 to Tang, et al. ("Tang"). These rejections are respectfully traversed if applied to the amended claims and in view of the accompanying evidence showing unexpected results and a teaching away from in the prior art. The references previously submitted in this regard are:

Reference submitted with the amendment and response filed on May 8, 2007

Vacanti, et al., *J. Pediatric Surgery* 23(1):3-9 (1988)

Shinoka, et al. *Circulation*, 94(9 Suppl):II164-8 (1996) (Abstract)

Reference Submitted with the Amendment and Response filed on September 18, 2008

Mol, et al., *Circulation*, 114(Suppl 1):152-158 (2006)

Schmidt, et al., *Swiss Med Wkly*, 135:618-23 (2005)

Legal Standard for Unpatentability Under 35 U.S.C. § 103(a)

When applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims at issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary considerations.

Graham v. John Deere, 383 US 1, 17-18, 148 U.S.P.Q. 459, 467 (1966). These four factors are traditionally referred to as the "Graham factors". The Graham factors were affirmed by the U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

Evidence of secondary considerations to be considered in an analysis under 35 U.S.C. § 103 include commercial success, long felt but unresolved needs, failure of others, etc. M.P.E.P § 2145, *citing Graham*, 383 U.S. at 17, 148 U.S. P.Q. at 467. Evidence may also include evidence that the claimed invention yields unexpectedly improved properties or that the claimed invention possesses unexpected properties. M.P.E.P § 2145, *citing In re Dillon*, 919 F.2d 688, 692-93, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990).

Analysis

The claims are non-obvious over Mikos in view of Sparks or Jauregui, alone or further in view of Griffith-Cima

The Scope and Content of the Prior Art

U.S. Patent No. 5,514,378 to Mikos ("Mikos")

Mikos discloses biocompatible porous polymer membranes prepared by dispersing salt particles in a biocompatible polymer solution. Mikos discloses that a three dimensional structure can be manufactured from the membranes. The resulting three-dimensional foam or shape is a porous, biocompatible matrix to which cultured cells can attach and proliferate, and can be used for organ transplant or reconstructive surgery (Mikos, column 3, lines 25-45).

U.S. Patent No. 3,514,791 to Sparks ("Sparks")

Sparks describes a die into which is placed a DACRON™ mesh secured to a stainless steel supporting ring (see column 5, lines 18-24). The die consists of a tube and mandrel (col. 3, lines 29-31). The die may be seeded with cells to make special parts, periosteal cells being used to make bone and epithelial cells being used to make epithelial tissue (abstract). Figures 6-12 illustrate a die for growing a tricuspid heart valve. Sparks further discloses that natural body processes produce the necessary connective tissue to fill the die cavity and form the valve graft (see column 2, lines 27-32 and column 5, lines 32-36). This is not a matrix which is formed of a synthetic biodegradable polymer, shaped for the cells to grow throughout the matrix to form a heart valve or leaflet.

U.S. Patent No. 4,795,459 to Jauregui ("Jauregui")

Jauregui discloses an implantable prosthetic device made of a biocompatible polymer and having a substantially continuous layer of autologous living cells attached via oligosaccharide-

lectin recognition linkages (abstract). The polymer is Teflon, Dacron, polyurethane or a polymer of a compound from the Krebs Cycle (Jauregui, col. 1, lines 50-56). **These are not biodegradable polymers.** The surfaces of the polymers are processed to provide COOH or NH2 groups for covalently attaching lectins which are used to attach endothelial cells to the prosthetic device. Jauregui further discloses a method of implanting a prosthetic device which comprises removing cells from a patient, attaching them to a polymer via oligosaccharide lectin recognition linkages, growing the cell layer on the surface, and implanting the device in the patient (Jauregui, col. 1, lines 58-65). This is not a matrix where the cells grow throughout the matrix to the edges.

U.S. Patent No. 5,709,854 to Griffith-Cima, et al. ("Griffith-Cima")

Griffith-Cima discloses a cell-polymeric **solution,** which is injected into an animal to form a polymeric hydrogel containing dispersed cells (Griffith-Cima, Abstract). Griffith-Cima discloses that the cell-matrix can be combined with humoral factors such as growth factors, to promote cell transplantation and engraftment (Griffith-Cima, col. 5, lines 45-60).

Ascertaining the differences between the prior art and the claims at issue

Claim 1 defines a method of making a cell-matrix construct for use as a heart valve or leaflet, comprising

implanting into an animal a cell-matrix construct comprising a fibrous matrix in the shape of a heart valve or heart valve leaflet,

wherein the matrix is formed of a biocompatible, biodegradable polymer

having seeded therein cells selected from the group consisting of endothelial cells, myofibroblasts, skeletal muscle cells, vascular smooth muscle cells, myocytes, fibromyoblasts, and ectodermal cells,

wherein the synthetic biodegradable polymer provides the biomechanical properties of a heart valve or leaflet until the seeded cells can lay down their own extracellular matrix, and

the matrix is formed so that the cells attach to and proliferate on it to the edges of the matrix.

Mikos does not disclose a method for making a heart valve. However, the Examiner alleged that Mikos discloses every element of the claims except for the disclosure of the matrix to be in the form of a heart valve or heart valve leaflet (Office Action mailed on June 18, 2008, page 5, para. 1). Applicants respectfully disagree, especially in view of the amendments discussed above to further define the differences. Mikos, in addition to not disclosing a matrix in the form of a heart valve or a heart valve leaflet, does not disclose a cell-matrix construct where the polymers are biodegradable but provide the biomechanical properties to withstand repeated stress and strain *in vivo* until the cells have formed new extracellular matrix. None of Sparks or Jauregui makes up for this deficiency.

The Examiner cited to Vacanti, et al., *J. Pediatric Surgery* 23(1):3-9 (1988) ("Vacanti 1") (cited in Mikos (at col. 2, lines 15+)) which discloses that a scaffold should mimic its natural counterpart (Office Action, page 5, para. 1) as supplying the missing disclosure in Mikos. However, the Examiner has mischaracterized the disclosure in Mikos, as well as the disclosure in

Vacanti 1. Mikos, at col. 2, lines 28-35 states "Moreover, they (i.e. Vacanti 1) recognized the advantage of using synthetic biodegradable polymer substrates to form a scaffold that *mimics its natural counterpart*, the ECM of the body, serving both a physical support and an adhesive support for parenchymal cells...". Applicants are not claiming parenchymal cells. The ECM of the parenchyma is not shaped like a heart valve or heart valve leaflet, nor are organs such as liver or intestine subject to repeated stress and strain, requiring flexibility, strength, and other biomechanical properties that must persist, even as the polymer degrades.

The Examiner further alleged that Mikos suggests tailoring the bioabsorbable matrix according to the selected biological tissue to be grown, citing to Mikos, col. 13, lines 31+ (Office Action mailed June 18, 2008, page 6, para. 2). Mikos, at col. 13, lines 31+, discloses that the membranes are processed into anatomical shapes, or foams, for use in reconstructive surgery or organ transplantation. However, all Mikos describes is a polymer composition which is molded into different **forms and shapes** and processes for making these forms porous. Thus, Mikos discloses matrices having a particular shape; **not** function. There is no disclosure that one can form a structure that can move and function as the structure to be replaced, such as a heart, which must move repeatedly, be elastic and flexible, and withstand enormous strain. The Examiner cited to Mikos, col. 4, lines 49-54, for disclosure relevant to matrices having the desired **function** of a particular tissue (Office Action page 7, para. 1). It is unclear how the Examiner arrived at this conclusion. Mikos discloses how three dimensional structures are formed into a desired shape, and states, "a particular advantage of the use of the membranes is that polymers with

different properties and membranes with different porosities can be used to assemble the structure, much as it occurs in nature" (*See* Mikos, col. 4, lines 51-55). One can assemble a structure as it **occurs** in nature. However, this is not tantamount to assembling a structure which *functions as it functions in nature.* The Examiner's attention is drawn to Mol, et al., *Circulation*, 114(Suppl 1):152-158 (2006) ("Mol") and Schmidt, et al., *Swiss Med Wkly*,135:618-23 (2005) ("Schmidt") (copies of which are attached for the convenience of the examiner). As discussed in Schmidt and Mol, prior to 1995, the art had seen some success in making heart valves as they occur in nature; the challenge was getting them to function accordingly.

Although the Examiner admitted that Mikos is silent about vascular tissue, the Examiner asserted that the use of tissue engineering employing both resorbable and nonresorbable polymer scaffolds to replace diseased tissue, including vascular tissue, is known in the art, citing Sparks and Jauregui (Office Action mailed 6/18/08, page 7, last para.). The Examiner also asserted that the fact that these polymers can be molded to mimic the shape of the tissue to be engineered is also known in the art (*citing* Mikos, col. 13+). However, this does not make obvious the claimed method, which results in a cell-matrix construct that can withstand repeated stress and strain. The Examiner's attention is drawn to the disclosure in Mol and Schmidt (discussed above) - availability of materials to make heart valves does not make obvious methods of making heart valves with the requisite properties.

With respect to Jauregui (as quoted by the Examiner on page 8 of the Office Action), Jauregui discloses that it may be desirable to provide a layer of cells on a surface of an implanted

prosthetic device (made of a biocompatible polymer) e.g., implantable cardiovascular devices, e.g., vascular prosthesis, artificial hearts, and heart valves. According to Jauregui, this would allow complete endothelialization, preventing thrombo-embolic episodes (*See* Jauregui, col. 1, lines 10-19). Jauregui discloses a method for attaching living cells onto the surface of the device using lectin recognition linkages (See Jauregui, col. 1, lines 41-46). Thus, Jauregui discloses a material having cells seeded on the surface, not within a matrix. Furthermore, Jauregui does not disclose how to make a cell-matrix construct for use as a heart valve, wherein the cell-matrix construct can withstand repeated stress and strain. The only disclosure with respect to shape in Jauregui is found in the claims. Jauregui claims an implantable prosthetic device comprising a member that has a shape to perform a cardiovascular function when implanted (Jauregui, claim 1). Claim 7 in Jauregui specifies that the member is a tubular vessel that is sufficiently small to function as a coronary artery. There is no disclosure of implanting a device in the shape of a heart valve. Thus, Jauregui does not make up for the deficiencies in Mikos. Sparks discloses a method that involves implanting a *stainless steel die* in an animal, and similarly does not make up for the deficiencies in Mikos.

With respect to Sparks, Sparks discloses implanting a *stainless steel die* in an animal, containing a reinforcing mesh; connective tissue entering the die cavity encapsulates the reinforcing mesh therein, and completely fills the die cavity to form a valve graft (*See* Sparks, col. 5, lines 32-34). The stainless steel in Sparks is essential for the method disclosed therein. However if one were simply to replace the DACRON™ mesh (which is NOT biodegradable) in

the die of Sparks with the biodegradable polymers disclosed in Mikos, one would not arrive at the claimed method. Sparks does not disclose a method that results in a cell-matrix construct that can withstand repeated stress and strain. Furthermore, Sparks teaches away from such a replacement of the DACRON™ mesh disclosed therein with the biocompatible polymer disclosed in Mikos. Sparks depends on the inherent rejection phenomenon of the body (i.e., rejection of the DACRON™ mesh), to encapsulate the mesh in the die such that the die cavity becomes completely filled with connective tissue **and thereby form a replacement part** (emphasis added) (*See* Sparks, col. 2, lines 9-17). Sparks in col. 1, lines 45-56 describes this phenomenon of foreign body rejection in simple terms, as incompatibility with a patient's body. Thus, Sparks requires a non-biocompatible polymer. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or **would be led in a direction divergent from the path that was taken by the applicant (emphasis added)**. In re Gurley, 27 F.3d 551 (Fed. Cir. 1994). One or ordinary skill in the art would not be motivated to modify the method of making a heart valve disclosed in Sparks, to include the biocompatible polymers disclosed in Mikos, since the non-biocompatibility of the polymer is necessary to make the heart graft as disclosed in Sparks. Thus, one would be led away from biocompatible polymers required by the claims.

For at least the reasons stated above, a combination of the prior art does not disclose all the elements in the claims. Furthermore, the Examiner has provided no evidence to back the allegation that the results yielded by the claimed method (i.e. a cell-matrix construct that can

withstand repeated stress and strain, and function as a heart valve or leaflet) would have been predictable from the prior art. In fact, the disclosure in Schmidt and Mol (discussed above), with respect to the challenges of getting heart valve grafts to function accordingly prior to 1995, contradicts this allegation. Notably, the Sparks patent issued 25 years prior to 1995, and the Jauregui patent issued 6 years prior to 1995.

Making a structure with the requisite mechanical physical and mechanical properties necessary for biological function, especially a structure such as a heart valve, had been a challenge, and was neither disclosed by nor predictable at the time this application was filed (see Schmidt and Mol). Claim 1 requires the synthetic biodegradable polymer provide the biomechanical properties of a heart valve or leaflet until the seeded cells can lay down their own extracellular matrix, and the matrix be formed so that the cells attach to and proliferate on it to the edges of the matrix. This is a critical limitation of a claim to a construct which is to be used to replace a heart valve or heart valve leaflet, structure which must open and close hundreds of times every hour, thousands of times every day, for years. Mikos is silent about heart valves, and therefore does not disclose or suggest how to make valves which can withstand repeated stress and strain. None of Sparks or Jauregui makes up for this deficiency. As stated in the MPEP, § 2141.02) "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)". The Examiner cannot use

hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. In re Fine, 837 F.2d 1071 (Fed. Cir. 1988); see also, KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398 (U.S. 2007) at § 1542.12.

The Examiner alleged that the resulting tissue produced by Mikos as modified, is designed to be a tissue counterpart to be used in the heart as a valve or portion thereof, and would reasonably have the structure and function of its tissue counterpart. According to the Examiner, such tissue would possess the properties of elasticity, flexibility and strength corresponding to the native tissue. Applicants respectfully disagree. It appears as though the Examiner is concluding that any engineered tissue necessarily has all the properties of the native tissue simply because it was intended to replace that tissue. If that were the case, the breakthrough in tissue engineered valves would not have been as late as 1995 (as stated in Mol and Schmidt), in view of the numerous attempts in the past and availability of tissue engineering tools well before 1995. As noted in Schmidt, many of the available heart valve prosthesis did not actively adapt to the physiological environment such as pressure changes and mechanical demands, because they remained inherently different from the tissue they replaced (see Schmidt, first page, left. col. 2nd para.). Therefore, one cannot conclude that simply because a structure is meant to replace a heart valve it would have all the properties of the heart valve, especially the ability to withstand pressure changes and mechanical demands (i.e. repeated stress and strain). Schmidt further discloses these limitations motivated the exploration of novel approaches towards valve replacement. Schmidt goes further to cite the studies by Shinoka (in 1995) as the

first milestone in heart valve tissue engineering (see Schmidt, first page, right col. 2nd para.). There is nothing in any of Mikos, Sparks or Jauregui that would lead one of ordinary skill to this functional limitation, i.e. a cell-matrix construct that can withstand repeated stress and strain; this is not an inherent characteristic of any and every device intended to replace a heart valve.

For at least the reasons set forth above, claims 1, 2, 5, 9-11, and the cell-matrix construct made according to the methods of claims 1, 2, 5, and 9-11 are non-obvious over a combination of Mikos with Sparks or Jauregui.

Claims 3 and 15/3

Claim 3 depends on claim 1, and specifies that the matrix is first cultured at a first site in a patient prior to being transplanted to a second site. Claim 15/3 defines the cell-matrix construct of claim 3.

For at least the reasons set forth above, the method of claim 3 and the cell-matrix construct made according to the method of claim 3 are non-obvious over a combination of Mikos with Sparks or Jauregui.

Claims 8 and 15/8

Claim 8 depends on claim 5 and specifies that the heart valve has mechanical strength, and flexibility or pliability. Claim 15/8 defines the heart valve of claim 8.

For at least the reasons set forth above, the method of claim 8 and the cell-matrix construct made according to the method of claim 8 are non-obvious over a combination of Mikos with Sparks or Jauregui.

(ii) The Claims are non-obvious over Mikos in view of Sparks or Jauregui and further in view of Cima-Griffith.

Claims 12, 13

Claim 12 depends on claim 1 and specifies that the cell-matrix construct includes growth factors. Claims 13 depends on claim 12 and specifies that the growth factors are selected from the group consisting of heparin binding growth factor (HBGF), transforming growth factor alpha or beta (TGF), alpha fibroblastic growth factor (FGF), epidermal growth factor (EGF), vascular endothelium growth factor (VEGF), insulin, glucagon, estrogen, nerve growth factor (NGF) and muscle morphogenic factor (MMP).

The Examiner relied on Griffith-Cima for disclosing that growth factors can be included in a cell-matrix construct (Office Action mailed June 18, 2008, page 10). However, for at least the reasons set forth above, the method of claim 12 and the cell-matrix construct made according to the method of claim 12 are non-obvious over a combination of Mikos with Sparks or Jauregui, and further in view of Griffith-Cima. Griffith-Cima does not make up for the deficiencies of a combination of Mikos with Sparks, or Mikos with Jauregui.

Claims 14 and 15/14

Claim 14 depends on claim 1 and specifies that the cell-matrix further comprises bioactive factors incorporated to between one and 30% by weight. Claim 15/14 defines the cell-matrix construct made according to the method of claim 14.

The Examiner relied on Griffith-Cima for disclosing that growth factors can be included in a cell-matrix construct (Office Action mailed June 18, 2008, page 10). However, for at least the reasons set forth above, the method of claim 12 and the cell-matrix construct made according to the method of claim 12 are non-obvious over a combination of Mikos with Sparks or Jauregui, and further in view of Griffith-Cima. Furthermore, Griffith-Cima does not disclose incorporating growth factors into the cell-matrix construct between one and 30% by weight. The Examiner provided no reasons why one of ordinary skill in the art would modify the disclosure in Griffith-Cima to arrive at the growth factor concentration range recited in the claims.

(iii) The Claims are non-obvious over Sparks in view of Mikos or Griffith-Cima and in view of either Jauregui or Tang.

The Scope and Content of the Prior art

Sparks

Sparks is discussed above.

Mikos

Mikos is discussed above.

Griffith-Cima

Griffith-Cima is discussed above.

Jauregui

Jauregui is discussed above.

Tang

Tang discloses totally or partially bioabsorbable devices capable of degrading into biologically innocuous components.

Ascertaining the differences between the prior art and the claims at issue

Claims 1, 2, 5, 9-11, 15/1, 15/2, 15/5, 15/9, 15/10, and 15/11

Claim 1, drawn to a method of making a cell-matrix construct for use as a heart valve or leaflet requires the synthetic biodegradable polymer provide the biomechanical properties of a heart valve or leaflet until the seeded cells can lay down their own extracellular matrix, and the matrix be formed so that the cells attach to and proliferate on it to the edges of the matrix.

Sparks does not disclose a method for making a cell-matrix construct for use as a heart valve which involves implanting into an animal a cell-matrix construct comprising a fibrous matrix in the shape of a heart valve or heart valve leaflet. Sparks does not disclose a matrix wherein the matrix is formed of a biocompatible, biodegradable polymer having cells seeded therein. Sparks does not disclose a method for making a cell-matrix construct requiring the synthetic biodegradable polymer provide the biomechanical properties of a heart valve or leaflet until the seeded cells can lay down their own extracellular matrix, and the matrix be formed so that the cells attach to and proliferate on it to the edges of the matrix.. Sparks does not disclose seeding cells into a cell-matrix construct for use as a heart valve graft. A combination of Sparks with Mikos, Griffith-Cima, Jauregui or Tang does not make up for these deficiencies.

The Examiner alleged that Sparks discloses a fibrous polymeric matrix in the shape of a heart valve, directing Applicants to Sparks, col. 5, lines 5-75 (Office Action mailed June 18,

2008, page 11, para. 3). This is incorrect. Sparks discloses a stainless steel die for growing a tricuspid valve (col. 5, line 7), with holes through which connective tissue enters the die cavity encapsulating the mesh reinforcing member (51) **and completely fills the die cavity to form a heart valve graft (60) (shown in Figure 12), which is similar in shape to the reinforcing member** (51) (Sparks, col. 5, lines 32-36); the heart valve graft is similar in shape to the reinforcing member; the shape of the reinforcing member is not disclosed and "similar" is not characterized. The only polymeric material used in Sparks is DACRON™ mesh (i.e., the mesh reinforcing member). Thus, it is unclear how the Examiner arrive at the conclusion that the polymeric matrix in the shape of a heart valve. Moreover, the mesh is not biodegradable, and therefore remains part of the construct indefinitely, interfering with its function.

There is no disclosure in Sparks that DACRON™ mesh is formed in the shape of a heart valve, nor can one of ordinary skill conclude that the disclosure in Sparks, of putting DACRON™ mesh (cloth) in the cavity formed between the stainless steel die pieces, is the same as forming a DACRON™ mesh in the shape of a heart valve. The Examiner cited to Figure 7, which according to the Examiner, shows reinforcing mesh 51 approximating the shape of the die forming leaflets (Office Action mailed June 16, 2008, page 12, para. 1). This is not the same as the reinforcing mesh having the shape of a leaflet. The Examiner cannot separate the features disclosed in Sparks or read into Sparks' elements that are not disclosed therein. The Examiner also alleged that Sparks at col. 5, lines 32-36 and 55-60, clearly teaches that the mesh has the same configuration as the die cavity (Office Action mailed June 16, 2008, page 12, para. 1).

Applicants are unclear as to the metes and bound of "same configuration" as used by the Examiner. However, the claims require the biodegradable polymer to be in the shape of a heart valve or leaflet. Sparks at col. 5, lines 32-36 states, "Connective tissue entering the die cavity through perforation **41** encapsulates the mesh reinforcing member **51** and completely fills the die cavity to form a heart valve graft **60** in Figure 12, which is similar (emphasis added) in shape to the reinforcing member **51** in Figure 9" **–the valve graft is similar in shape to the DACRON™ mesh, it is unclear from the cited section in Sparks, what that shape is.** Sparks at col. 5, lines 55-60, further states, "this (i.e., the three edges of valves retreating away when the valve is open) is also illustrated in Figure 9, wherein the upper edge portions **65** of the reinforcing mesh are shown in the same configuration they assume in the die cavity, the latter (i.e., die cavity) having approximately the configuration assumed by the leaflets of the graft in the open position". This is not a disclosure of a DACRON™ mesh shaped in the form of the leaflets.

The Examiner relied on Mikos and Griffith-Cima and Tang for providing a biodegradable matrix. However, substituting the non-biodegradable DACRON™ mesh in Sparks with biodegradable polymers does not arrive at the claimed method for at least the reasons stated above. Importantly, Sparks teaches away from such a modification. In addition, substituting the non-biocompatible DACRON™ mesh within the die cavity in Sparks with a biocompatible polymers of Mikos, Griffith-Cima, or Tang would materially change the principle of operation of the method disclosed in Sparks; the non-biocompatible property of DACRON™ mesh disclosed in Sparks is required for the formation of the graft disclosed therein (See Sparks col. 2, lines 9-

16). A combination of Sparks with any of Mikos, Griffith-Cima, or Tang is therefore impermissible under 35 U.S.C. § 103 (a) (See MPEP §2143.01). Similarly, a combination of Jauregui (which discloses biocompatible polymers) with Sparks is impermissible 35 U.S.C. § 103 (a); however, even if such a combination were possible, it does not arrive at the claimed method.

With respect to cells seeded in the polymeric matrix, Sparks is silent about seeding cells in valve grafts. The Examiner has not cited to any disclosure in Sparks with respect to seeding cells in valve grafts.

There is no similarity whatsoever between the method disclosed in Sparks and the method defined by claim 1. The only similarity between Sparks and the claims is the **name** of the resultant product. There is no similarity in the process of making, or the materials used, therefore it is expected that there would be no similar physical properties.

The Examiner cited to Mikos, alleging a disclosure by Vacanti 1, that the scaffold should mimic the natural tissue counterpart, and that Vacanti 1 provides evidence that better results are obtained when the matrix is first implanted, prevascularized and then seeded with select cell, attaching the relevant portion of Mikos (Mikos column 2, lines 16-44). Vacanti 1 is discussed above with respect to "mimicking the natural tissue counterpart". It is not clear what Mikos means by "better results" (cited by the Examiner); however, since Mikos is referring to Vacanti 1, the "better results" obtained are not concerned with a graft that can withstand repeated stress and strain, since Vacanti 1 is only concerned with enhancing viability of large numbers of

transplanted cells seeded onto an amorphous fibrous support structure (a gauze). It is clear from the discussion in Vacanti 1 that Vacanti 1 cannot make obvious the claimed method, which provides heart valves wherein the synthetic biodegradable polymer provides the biomechanical properties of a heart valve or leaflet until the seeded cells can lay down their own extracellular matrix, and the matrix is formed so that the cells attach to and proliferate on it to the edges of the matrix. Vacanti 1 does not recognize the problem with somehow providing the cell matrix with mechanical properties such as strength, flexibility, resistance to strain – features essential for a structure which will be opened, closed, and subjected to pressures every second, every hour, every day, every month, every year in the individual's life following implantation. There are simply no comparable requirements when it comes to a parenchymal tissue such as a liver or pancreas. However, for at least the reasons stated above, a combination of Mikos with Sparks is impermissible under 35 U.S.C. § 103 (a)

The Examiner also asserted that the materials used by Applicants are well known, and known equivalents are taught by Jauregui or Tang, and, that Tang teaches that bioresorbable materials play a critical role in fabrication of devices used for tissue regeneration (Office Action mailed June 118, 2008, page 15). Applicants respectfully disagree with the Examiner's allegation of equivalency. For at least the reasons that Sparks needs the DACRON™ mesh (i.e., ability to be rejected by the body), the biocompatible polymers disclosed in Jauregui or Tang are not equivalent to the DACRON™ mesh required by the method in Sparks (*See* MPEP §2144.06). Even if they were equivalent, the issue here is not merely using biodegradable materials to make

heart valves. That biodegradable materials can be used in tissue engineering is known in the art, as correctly stated by the Examiner. It is also known that polymers can be molded to mimic the shape of the tissue to be engineered. However, making a structure with the requisite mechanical physical and mechanical properties necessary for biological function has been the challenge- *See* Mol and Schmidt.

Even if one could combine the prior art as the Examiner has done, the claims do not merely define a method that can be accomplished by substituting the DACRON™ mesh in the stainless steel die of Sparks, with the biodegradable materials disclosed in Jauregui or Tang, or the use of the materials disclosed in Jauregui or Tang, shaped into a three dimensional structure. Claim 1 requires the cell-matrix construct be able to withstand repeated stress and strain - i.e., *to have the biomechanical properties to function as a heart valve or leaflet*; the claimed method steps arrive at a heart valve with this characteristic. This is a critical limitation of a claim to a construct which is to be used to replace a heart valve or heart valve leaflet, structure which must open and close hundreds of times every hour, thousands of times every day, for years.

However, according to the Examiner the device of Sparks, as modified, would inherently possess the properties that would be capable of withstanding cyclic stresses and strains, since the valve is designed to function as a replacement of a natural valve (Office Action mailed June 18, 2008, page 16, para. 2). The Examiner must provide a technical reason for a conclusion of inherency. According to the MPEP §2112, "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the

reference, and that it would be so recognized by persons of ordinary skill. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. "*In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)". As demonstrated by Shinoka, et al. *Circulation*, 94(9 Suppl):II164-8 (1996) ("Shinoka 1", abstract attached to the amendment and response filed on May 8, 2007), the property of withstanding stress and strain is not inherent in biodegradable polymers, therefore merely replacing the DACRON™ mesh in Sparks with biodegradable polymers does not guarantee this characteristic. None of the cited references disclose that the biodegradable polymers necessarily possess the ability to withstand repeated stress and strain or how to adapt these polymers to have the requisite property. In fact, Shinoka 1 demonstrates this point. Furthermore, at least from the disclosure in Mol (page I-152, left col.) which states, "The first successful replacement of a single pulmonary valve leaflet with a tissue-engineered equivalent, based on a synthetic biodegradable scaffold was demonstrated in lambs in 1995. As a major milestone toward clinical application, tissue-engineered tri-leaflet heart valves were shown to function successfully in sheep for up to eight month", it is apparent that designing a prosthetic to function as a heart valve does not automatically impart upon it the ability to function as one; as previously noted, numerous studies prior to 1995, had designed heart valves. The Examiner's allegation of inherency is unfounded.

With respect to the Examiner's allegation (Office Action mailed June 18, 2008, page 16, para. 2), that replacing the non-biodegradable mesh with a biodegradable mesh would eventually

produce a tissue replacement having only natural confluent cells in the form of vascularized tissue which is essentially an equivalent counterpart to the natural tissue, and that it is a reasonable expectation that the tissue equivalent would possess the structure and function of its tissue counterpart, the Examiner's attention is drawn to the discussion of the disclosure in Mol and Schmidt above.

There is no motivation to combine the references as the Examiner has done, nor would it result in the claimed invention, much less do so predictably

There is no motivation to combine these references as the Examiner has done, nor would one skilled in the art have a reasonable expectation of success if one did so, based on the art, to yield a structure which can withstand repeated stress and strain.

As discussed above, Sparks teaches away from such a modification. In addition, substituting the non-biocompatible DACRON™ mesh within the die cavity in Sparks with a biocompatible polymers of Mikos, Griffith-Cima, Jauregui or Tang would materially change the principle of operation of the method disclosed in Sparks.

A skilled artisan would not be motivated to combine Mikos, Jauregui, Tang or Griffith-Cima with Sparks to arrive at the claimed method and construct, much less have a reasonable expectation of success. According to the MPEP §2143.01, "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the **desirability** of the combination".

Applicants have unexpected results

The most fundamental reason why the claimed subject matter is patentable is that no one could have predicted, nor have reasonable expected, a synthetic polymeric matrix seeded with cells to form a functioning heart valve or leaflet that could not only provide the required function - essential to life itself - and become integrated into the host after transplantation, so that it continued to provide the essential function for the host to live.

For decades, people had tried to make artificial hearts, relying on machines, processed animal or cadaver heart valves, and combinations thereof, just as the art cited by the examiner demonstrates. However, applicants were the first to figure out how to make this technology actually work. The showed that the structures could function just as the native tissue and could integrate into ***and grow with the host***, to provide a cure, not just a replacement component, for the heart valve or leaflet that was being replaced.

The examiner's attention is drawn to the enclosed references which show, step by step, how they have shown that one can make the matrices as claimed, using different synthetic biodegradable materials, seeded with different cell types, cultured *in vitro* or *in vivo*, then implanted into large animal models (lambs) to demonstrate that they can form heart valves and leaflets that are histologically comparable to native tissue, functionally comparable to native tissue, integrate into a natural heart, and grow with the heart.

Results of this magnitude must be considered in making a rejection under 35 U.S.C. 103. The Supreme Court has made it clear that if the outcome could not have been predicted, based on the prior art by one of ordinary skill in the art at the time the application was filed, it is not

obvious. The results obtained with the claimed method were not predictable. They are important and applicants should be re-granted a patent with claims having sufficient scope to allow the further development of this technology so it will be made available to those in need.

For the foregoing reasons, Applicants submit that claims 1-5, 8, 11-14, 18 and 19 are patentable.

Respectfully submitted,

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